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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/529,795	04/20/2000	HARTMUT KUPPER	0480/001178	4157

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EXAMINER	
SEHARASEYON, JEGATHEESAN	
ART UNIT	PAPER NUMBER
1647	

DATE MAILED: 12/17/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/529,795	KUPPER ET AL.	
	Examiner	Art Unit	
	Jegatheesan Seharaseyon	1647	

-- *The MAILING DATE of this communication appears on the cover sheet with the correspondence address* --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *24 September 2003*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-7* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-7* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. §§ 119 and 120

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

13)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application) since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

a) ☐ The translation of the foreign language provisional application has been received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121 since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____.
4) ☐ Interview Summary (PTO-413) Paper No(s). _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

1. This office action is in response to the reply filed on 9/24/03. Claims 1-6 are pending.

2. The text of those sections of Title 35, U. S. Code not included in this action can be found in a prior Office Action.

Claim Rejections - 35 USC § 112, second paragraph withdrawn

3. Applicants arguments filed on 9/24/03 are persuasive with respect to the rejection of claims 1-7 under USC § 112, second paragraph for being vague and indefinite in the recitation of the term "measurement period". Therefore, the rejection is withdrawn. However, see new grounds of rejection below.

New Claim Rejections - 35 USC § 112

4. Claims 1-4 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

4a. Claim 1 rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential steps, such omission amounting to a gap between the steps. See MPEP § 2172.01. The omitted steps are: Applicant intends to measure IL-6 increase over a period of time, however there is no method step to measure the increase in IL-6. Claims 2-4 are rejected insofar as they depend on rejected claim 1.

4b. Claim 1 is rejected as vague and indefinite because it is not clear what septic disorders the Applicant contemplates.

4c. Claim 2 is rejected as vague and indefinite because it is unclear how serum IL-6 can be both 500pg/ml and above in the same measurement period.

Claim Rejections - 35 USC § 101

5. 35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

5a. Claim 7 is rejected under 35 U.S.C. 101 because waiting to establish the IL-6 level in a patient with sepsis will be injurious to the patient (Stenzel et al., U.S. Patent No: 6, 235, 281, Fig 1A) .

New Claim Rejections - 35 USC § 102

6. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

The changes made to 35 U.S.C. 102(e) by the American Inventors Protection Act of 1999 (AIPA) and the Intellectual Property and High Technology Technical Amendments Act of 2002 do not apply when the reference is a U.S. patent resulting directly or indirectly from an international application filed before November 29, 2000. Therefore, the prior art date of the reference is determined under 35 U.S.C. 102(e) prior to the amendment by the AIPA (pre-AIPA 35 U.S.C. 102(e)).

6a. Claims 1-2 and 4 are rejected under 35 U.S.C. 102(e) as being anticipated by Stenzel et al. (U.S. Patent No: 6, 235, 281)

The applied reference has a common inventor with the instant application. Based upon the earlier effective U.S. filing date of the reference, it constitutes prior art under 35 U.S.C. 102(e). This rejection under 35 U.S.C. 102(e) might be overcome either by a showing under 37 CFR 1.132 that any invention disclosed but not claimed in the reference was derived from the inventor of this application and is thus not the invention "by another," or by an appropriate showing under 37 CFR 1.131.

The instant invention is directed to the use of TNF antagonists for the production of drugs for the treatment of septic disorders characterized by elevated serum levels of interleukin-6 (IL-6).

Stenzel et al. teaches a method of treating a patient with septicemia (a septic disorder) with elevated IL-6 levels (above 1000pg/ml) by administering TNF antagonist. They also teach that the TNF antagonist used is a F $(ab')_2$ fragment of a monoclonal anti-TNF antibody (column 3, lines 39-40). Please note that the examiner is considering, in view of the specification, the IL-6 levels indicated in claim 1 of U.S. Patent No: 6,235,281 to be 1000pg/ml and not 1.000p/ml. The levels of IL-6 in '281, are clearly above the 500pg/ml threshold of the instant claims. In addition, Patent '281 teaches that a distinct reduction in mortality is observed when the speticemic patients who are treated have IL-6 levels of 500 pg/ml or more at the start of the treatment (column 2, lines 17-19). It is routine in the management of patients with chronic conditions, to monitor proinflammatory cytokines (IL-6) as markers over a period of time to determine the change in the levels. Therefore, the disclosure of Stenzel et al. anticipates claims 1-2 and 4.

Claim Rejections - 35 USC § 103, maintained

7. Claims 3 and 5-7 remain rejected under 35 USC § 103 as being obvious over Stenzel et al. (U.S. Patent NO: 6, 235, 281 or WO95/20978) in view of Kragsbjerg et al. (1996) for reasons set forth in Paper No: 12. Applicant's arguments filed on 9/24/03 have been fully considered but are not persuasive. Applicant alleges that the Office has not established a *prima facie* case of obviousness, motivation and a reasonable case expectation of success. Applicant assert that the presently claimed invention requires that the serum level of IL-6 increases in a measurement period of at least 30 minutes (see reply page 3, 2nd paragraph), however claim 1 does not actually require any measurement of IL-6 in the 30 mins. Further, Applicant alleges that the serum level increase is a necessary criterion for successfully identifying patients to whom TNF antagonists can be administered with heightened effect. Although not explicitly recited, the '281 patent recites that the "normal" Il-6 serum levels are usually below detection limits to a maximum of 20 pg/ml (see column 2, lines 28-30). It further teaches that septicemic patients with IL-6 levels of 500 pg/ml or more including levels above 1000 pg/ml respond well to the treatment with TNF antagonists (see column 2, lines 15-20). Thus, clearly recognizing the increase in serum IL-6 levels in septicemia patients and the use of TNF antagonist's in the treatment.

In addition, Applicant asserts that Stenzel "neither describes a change in IL-6 level, nor measurement of such a change in septicemia patients." It is also alleged that Stenzel et al. also "omits any reference to the relevance of the directionality of change in serum IL-6 levels over the course of the measurement period." It should be noted that

IL-6 levels in the serum would have been increasing regardless of whether it was measured or not. As described above it is clear that Stenzel et al. did measure the serum IL-6 levels in patients prior to the treatment with TNF antagonists. However, it is also clear from the Stenzel's teaching that although not explicitly recited it does recognize that an increase in serum IL-6 levels over a period of time (20 pg/ml to 1000 pg/ml) in patients with septicemia.

Applicant also asserts that Kragsbjerg reference does address the deficiencies of Stenzel et al. It is asserted that the reference does indicate anywhere that TNF antagonists would be desirable or effective in cases where IL-6 serum levels are increasing. Kragsbjerg reference was introduced by the Office to teach the measuring of IL-6 over a period of time. Stenzel et al previously taught the effectiveness of using TNF antagonists in treating spectecemia with increased serum IL-6 levels. Contrary to Applicants assertion that Kragsbjerg reference has only limited discussion on increase in IL-6, the reference teaches that "significantly higher levels of cytokines IL-6, Il-8 and TNF-alpha were found in patients with severe sepsis compared to the levels found in patients with less severe illness" (see page 396, 2nd paragraph). Therefore, Stenzel et al. (U.S. Patent NO: 6, 235, 281 or WO95/20978) in view of Kragsbjerg et al. (1996) is maintained.

Double Patenting

8. The rejection of claims 1-7 under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-3 of U.S. Patent No. U.S. Patent No: 6,235,281 in view of Kragsbjerg et al. (1996) is maintained. Applicant's arguments

filed on 9/24/03 have been fully considered but are not persuasive for reasons set forth in Paper No: 12 and above in paragraphs 5 and 6.

9. No claims are allowable.

Contact Information

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jegatheesan Seharaseyon whose telephone number is 703-305-1112. The examiner can normally be reached on M-F: 8:30-4:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Kunz can be reached on 703-308-4623. The fax phone number for the organization where this application or proceeding is assigned is 703-308-0294.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

JS

Lorraine Spector

LORRAINE SPECTOR
PRIMARY EXAMINER